Abstract

This study assessed the association of chronic conditions and multimorbidity with perceived stress among community-dwelling adults in 44 low- and middle-income countries. Data were analyzed from the World Health Survey (2002-2004) including 229,293 adults. A perceived stress score [range 0 (lowest stress) -100 (highest stress)] was computed based on two questions from the Perceived Stress Scale. Eleven chronic conditions were assessed. Multivariable linear regression analyses were conducted to explore the associations. All chronic conditions were associated with significantly higher mean perceived stress scores with the exception of edentulism. The association was particularly strong for depression (b-coefficient=14.71; 95%CI: 13.68, 15.74), visual impairment (b-coefficient=10.66; 95%CI: 8.09, 13.23), and schizophrenia (b-coefficient=9.98; 95%CI: 7.71, 12.24). Compared to no chronic conditions, the b-coefficients (95%CI) of perceived stress for 1, 2, 3, and ≥4 chronic conditions were 5.58 (4.94, 6.23), 9.58 (8.67, 10.49), 14.15 (12.63, 15.67), and 20.17 (18.29, 22.05) respectively. The associations with perceived stress were significantly stronger among the poorest for arthritis, asthma, diabetes, edentulism, and ≥4 chronic conditions. Our data suggest that a range of chronic conditions and multimorbidity are associated with greatly increased perceived stress among people in low- and middle-income countries, and that the poorest may be a particularly vulnerable group.

Keywords: perceived stress; multimorbidity; chronic conditions; poverty; low- and middle-income countries

Multimorbidity is typically defined as two or more chronic conditions and recent estimates have suggested that up to 72% of the general population has multimorbidity (1). The high prevalence of multimorbidity is predominantly attributed to the growing incidence of chronic conditions (2), coupled with the increasing life-expectancy, and it is without a doubt one of the most significant challenges faced by health care providers and policymakers (3, 4). Multimorbidity is associated with increased use of health care services (5), a lower quality of life (6), and a higher risk for premature mortality (7). Large-scale studies from single countries have demonstrated a clear socio-economic pattern with higher prevalence of multimorbidity being observed in socio-economically vulnerable settings (4).

This global evolving disease burden, along with a growing understanding of multimorbidity and its risk factors, requires the development of systems that integrate all aspects of health care, including the management of the psychological burden of chronic diseases (8) such as perceived stress. Perceived stress can be defined as feelings or thoughts that an individual has about how much stress they are under, as well as feelings about the uncontrollability and unpredictability of one's life, how often one has to deal with irritating hassles, how much change is occurring in one's life, and confidence in one's ability to deal with problems or difficulties (9). Chronic conditions may cause stress as a consequence of their symptoms, long-term prognosis, and other related issues such as treatment and its costs. Among people with chronic conditions, such as asthma, arthritis or diabetes, stress can intensify the effect of illness by increasing pain, functional limitations, and disability and decreasing adherence to medical treatment protocols, all of which may lead to psychological distress (i.e., a state of emotional suffering characterized by symptoms of depression and anxiety (10)), poorer health outcomes as well as increased risks of severe and chronic psychiatric and somatic complications (11-13). Moreover, perceived stress contributes significantly to higher mortality rates in a dose-response pattern (14), with even more stress-associated deaths evident among people with multimorbidity (15). These findings clearly suggest that people with multimorbidity are a particularly susceptible group for increased perceived stress.

To date, most of the research investigating associations between stress and chronic conditions or multimorbidity has however focused on stress within the context of psychological distress in high-income

countries. For example, an American study (16) including 110,455 adult participants, found that more psychological distress and mental illness were associated with higher probabilities for many chronic medical conditions but not for multimorbidity, although the association of psychological distress with mental illness and multimorbidity strengthened as the number of chronic medical conditions increased. To the best of our knowledge, there are no multinational representative population studies investigating associations between perceived stress, chronic conditions, and multimorbidity. In addition, there is an absence of such data from low- and middle-income countries (LMICs). This is an important research gap given the rapid increase in non-communicable diseases, mainly due to changes in lifestyles in these countries (17). Furthermore, the associations between chronic conditions or multimorbidity and perceived stress may differ in LMICs due to different disease profiles, limited treatment options and suboptimal treatment, or the high costs associated with treatment which may even lead to catastrophic expenditure, especially in poor households (18).

Given the aforementioned gaps within the literature, we set out to assess whether chronic conditions and multimorbidity are associated with higher perceived stress levels among community-dwelling adults in 44 LMICs, and to assess whether this association is stronger among poorer individuals. We hypothesized that higher stress scores would be associated with each chronic condition as well as higher numbers of chronic conditions, and that these associations would be stronger among the poorest people.

METHODS

Procedure

The World Health Survey was a cross-sectional, community-based study undertaken in 2002-2004 in 70 countries worldwide. Single-stage random sampling and stratified multi-stage random cluster sampling were conducted in 10 and 60 countries respectively. Stratification was conducted by gender, age, and residential area (rural/urban). Enumeration areas and households were also used as stratification units in the majority of countries. The detailed methodology of the survey has been provided elsewhere (19). Briefly, persons aged ≥18 years with a valid home address were eligible to participate. Each member of the household had equal probability of being selected with the use of Kish tables. The data were collected in all countries using the same questionnaire with some countries using a shorter version. The individual response rate (ratio of completed interviews among selected respondents after excluding ineligible respondents from the denominator) ranged from 63% (Israel) to 99% (Philippines) (20). Ethical approval to conduct this survey was obtained from ethical boards at each study site. Sampling weights were generated to adjust for the population distribution reported by the United Nations Statistical Division, and final post-stratification corrections were made to the sampling weights to account for non-response. Informed consent was obtained from all participants.

Chronic conditions

We assessed all chronic conditions for which information was available in the World Health Survey (i.e., 11 chronic conditions). Arthritis, asthma, and diabetes were based on self-reported lifetime diagnosis. For angina, in addition to a self-reported diagnosis, a symptom-based diagnosis based on the Rose questionnaire was also used (21). Chronic back pain was defined as having had back pain (including disc problems) every day during the last 30 days. Visual impairment was defined as having extreme difficulty in seeing and recognizing a person that the participant knows from across the road (i.e., from a distance about 20 meters) (22). A validity study showed that this response likely corresponds to World Health Organization definitions of visual impairment (23). The participant was considered to have hearing problems if the interviewer

observed this condition at the end of the survey. Edentulism was assessed by the question “Have you lost all your natural teeth?” Those who responded affirmatively were considered to have edentulism. A tuberculosis diagnosis was based on past 12-month symptoms and was defined as: (a) having had a cough that lasted for three weeks or longer; and (b) having had blood in phlegm or coughed up blood (23). Depression was defined using the Diagnostic and Statistical Manual of Mental Disorders-IV algorithm and was based on duration and persistence of depressive symptoms in the past 12 months using the same algorithms as in previous World Health Survey publications (24, 25). Finally, participants were asked whether they had ever been diagnosed of having schizophrenia or psychosis. Those who answered affirmatively were considered to have schizophrenia. While this question did not refer specifically to schizophrenia, for the sake of brevity, we use the term ‘schizophrenia’ throughout the text. We also calculated the total number of these conditions and classified it as 0, 1, 2, 3 and ≥4 conditions.

Perceived stress

In accordance with a previous World Health Survey publication (26), we assessed perceived stress in the last month with the use of two questions which were taken from the Perceived Stress Scale (27). The perceived stress scale is a widely used to measure stress sensitivity. The two questions from the scale have been validated and applied in many settings worldwide, including LMICs (26). The questions asked in the scale include: “How often have you felt that you were unable to control the important things in your life?”; and “How often have you found that you could not cope with all the things that you had to do?” The answer options to these questions were: never (score=1), almost never (score=2), sometimes (score=3), fairly often (score=4), very often (score=5). Since these answer options were an ordered categorical scale, as in previous World Health Survey studies, we conducted factor analysis with polychoric correlations to incorporate the covariance structure of the answers provided for individual questions measuring a similar construct (28). The principal component method was used for factor extraction, while factor scores were obtained using the regression scoring method. These factor scores were later converted to scores ranging from 0-100 (29) with

higher values representing higher levels of perceived stress. The mean (SD) score of this scale was 36.0 (27.4) (Skewness 0.38, Kurtosis 2.34).

Other variables

Data on sex, age (18-29, 30-39, 40-49, 50-59, 60-69, 70-79, ≥80 years), highest education achieved (no formal education, primary education, secondary or high school completed, or tertiary education completed), and country-wise individual-level wealth quintiles were also used in the analysis. The wealth quintiles were created using principal component analysis based on 15-20 assets including country-specific items for some countries.

Statistical analysis

Data were publically available for 69 countries. The data were nationally representative for all countries with the exception of China, Comoros, the Republic of Congo, Ivory Coast, India, and Russia. Countries without any sampling information (10 countries – Austria, Belgium, Denmark, Germany, Greece, Guatemala, Italy, Netherlands, Slovenia, UK) were excluded. Furthermore, 10 high-income countries (Finland, France, Ireland, Israel, Luxembourg, Norway, Portugal, Sweden, Spain, United Arab Emirates) were excluded as the focus of our study was on LMICs. Of the remaining LMICs, Brazil, Hungary, Turkey, and Zimbabwe were omitted as information on perceived stress was not collected. Furthermore, Georgia was also excluded due to a negative correlation between the two questions on perceived stress (26). Thus, the final analytical sample consisted of 229,293 people from a total of 44 countries. According to the World Bank classification in 2003, these countries corresponded to 20 low-income and 24 middle-income countries.

The statistical analysis was performed with Stata 14.1 (Stata Corp LP, College station, Texas). Information on perceived stress was missing from 7.2% of the sample while data on chronic conditions was missing from 5.6% (angina) to 18.4% (tuberculosis). We conducted multiple imputation of missing values using the *mi* commands in Stata using chained equations (20 imputations). The variables included in the imputation model were the outcome and all other covariates. The difference in mean perceived stress score

by the sample characteristic was tested by Student's *t*-test and one-way ANOVA for variables with two and three or more categories respectively. We conducted multivariable linear regression analysis to assess the association between each of the 11 chronic conditions or number of chronic conditions (exposure variables) and perceived stress score (outcome) while adjusting for sex, age, education, individual-level wealth, and country. For the analyses on the individual chronic conditions, we also adjusted for the presence of other illnesses in an attempt to obtain estimates that are less likely to be confounded by comorbid conditions. The variable on other illnesses was a binary variable (Y/N) and included information on whether the individual had any other chronic conditions apart from the chronic condition in question. A total of 12 separate models were constructed for each of the 11 chronic conditions and number of chronic conditions. In order to assess whether there is an interaction effect by individual-level poverty in the association between chronic conditions or number of chronic conditions and perceived stress, we also conducted interaction analysis by including an interaction term in the models [chronic condition (or total number of chronic conditions) X poverty (defined as the lowest individual-level wealth quintile)]. These analyses were adjusted for sex, age, education, other illnesses, and country.

All variables were included in the models as categorical variables with the exception of the perceived stress score (continuous variable). Adjustment for country was done by including dummy variables in the models, as in previous World Health Survey publications (28, 29). The sample weighting and the complex study design were taken into account in all analyses with the use of the *svy* command in Stata which uses the Taylor linearization method for robust variance estimation. We also conducted sensitivity analysis based on complete cases. The results obtained from the imputed and non-imputed datasets were very similar (data not shown). Results from the linear regression models are presented as b-coefficients with 95% confidence intervals (CIs). The level of statistical significance was set at $P<0.05$.

RESULTS

The overall mean age of the analytical sample was 38.3 years and 50.8% of the sample was female (Table 1). The full list of the included countries and their sample size can be found in the Appendix. The prevalence of ≥2 chronic conditions was 15.0%, with angina (15.1%) and arthritis (13.5%) being the most common chronic conditions. Female sex, older age, and lower levels of education and individual-level wealth were significantly associated with higher perceived stress scores and so were all of the 11 chronic conditions and higher numbers of chronic conditions. Higher stress scores were associated with an increase in the prevalence of all 11 chronic conditions and multimorbidity. Between perceived stress scores of <20 and 80-100, the prevalence of multmorbidity increased from 7.8% to 33.8% (Web Figure 1). Perceived stress increased with incremental numbers of chronic conditions where a clear pattern of heightened perceived stress scores associated with lower levels of individual-level wealth regardless of the number of chronic condition was observed, especially when the lowest and highest levels of individual-level wealth were compared (Web Figure 1).

The association between chronic conditions and perceived stress estimated by multivariable linear regression is illustrated in Figure 2. Compared to those without the condition, the mean perceived stress score was much higher for depression (b-coefficient=14.71; 95%CI: 13.68, 15.74), visual impairment (b-coefficient=10.66; 95%CI: 8.09, 13.23), and schizophrenia (b-coefficient=9.98; 95%CI: 7.71, 12.24). When compared to those with no chronic conditions, 1, 2, 3, and ≥4 chronic conditions were associated with 5.58 (95%CI: 4.94, 6.23; p<0.0001), 9.58 (95%CI: 8.67, 10.49; p<0.0001), 14.15 (95%CI: 12.63, 15.67; p<0.0001), and 20.17 (95%CI: 18.29,2 2.05; p<0.0001) higher mean perceived stress scores respectively (data shown only in text). The interaction effect of individual-level poverty and chronic conditions or number of chronic conditions on perceived stress is shown in Table 2. The associations between arthritis, asthma, diabetes, or edentulism and perceived stress were significantly stronger among those in the poorest individual-level wealth quintile compared to those who are wealthier. This was also the case when having 4 or more chronic conditions.

DISCUSSION

General findings

To the best of our knowledge, the current study is the first large-scale (n=229,293), multinational (44 LMICs) analysis that shows that chronic conditions and multimorbidity are associated with higher levels of perceived stress. Of interest, compared to those who were not in the poorest quintile, this association was significantly stronger among the poorest for arthritis, asthma, diabetes, edentulism, and ≥4 chronic conditions. In addition, higher levels of perceived stress were associated with higher prevalence of chronic conditions and multimorbidity, where between perceived stress scores of <20 and 80-100, the prevalence of ≥2 chronic conditions increased from 7.8% to 33.8%. Relatively few large-scale studies have investigated the relationship between perceived stress and multimorbidity. Nonetheless, a recent large scale study in Denmark (15) demonstrated that perceived stress was associated with an excess number of deaths among people with multimorbidity. Specifically, the authors noted that mortality hazard ratios (highest stress quintile vs. lowest) were 1.51 (95% CI: 1.25, 1.84) among persons without multimorbidity, 1.39 (95% CI: 1.18, 1.64) among those with 2 or 3 conditions, and 1.43 (95% CI: 1.18, 1.73) among those with 4 or more conditions even after adjustment for lifestyle factors and socioeconomic status. To our knowledge, there are no specific representative multinational studies investigating perceived stress and multimorbidity in the Western world or LMICs.

The exact mechanisms underlying perceived stress and several chronic conditions, and in particular, multimorbidity are in their infancy, and it is important that future work attempts to better understand these relationships. There are several hypotheses that may explain these findings. First, the association between higher levels of perceived stress and some chronic conditions as well as ≥4 chronic conditions was strongest among the poorest. It may be hypothesized that the poorest subgroup is not able to pay the treatment costs. Health-related expenditures impoverish an estimated 100 million people in LMICs each year (31). An estimated 50 million more suffer from catastrophic health expenditures, commonly defined as expenditures of 10% or more of income (31). Moreover, poorer persons spend a higher proportion of income on health care which might induce (financial) perceived stress (32), in particular following

catastrophic expenditure (33) or high out-of-pocket expenditure in areas with no health insurance (33), although this is not universal in all LMICs (34). Furthermore, treatments costs may increase the likelihood that patients in LMICs forgo needed treatment, in particular when there is a need for multiple medications, which are often prescribed to treat chronic diseases and multimorbidity (35). Untreated chronic conditions may increase the severity of the chronic condition or lead to further complications, which may increase levels of perceived stress. For example, untreated diabetes increases the risk for complications such as neuropathy, retinopathy, and nephropathy, which may further increase the disability level and resultant perceived stress. For edentulism, poorer people may be experiencing more stress due to suboptimal treatment (e.g., lack of dentures or implants). Next, it is also possible that stress precedes the development of chronic conditions. Chronic stress is known to lead to neuroendocrine dysregulation of the hypothalamic-pituitary-adrenal axis, which in turn may cause changes in the immune and inflammation system, and consequently lead to the development of chronic conditions and multimorbidity (36). These processes have been conceptualized as allostatic load (37, 38). Even subclinical perceived stress has been linked to changes in cortisol levels, the immune system response, and cortical reactivity (39). There is also evidence to suggest that perceived stress is a core feature of several mental illnesses. For instance, the relationship between perceived stress and depression has been observed previously (40). One should therefore consider that the strong relationship between depression and stress may in part be accounted for by some overlap in core symptoms (40). Finally, perceived stress may also lead to unhealthy behaviors, such as smoking, alcohol consumption, unhealthy dietary choices (41, 42) and a sedentary lifestyle (43), which might also be implicated in the development of chronic conditions. Of note, it was not possible to adjust for some of these important lifestyle factors, which may have influenced the relationships that we observed between stress and chronic conditions and multimorbidity. Future research is therefore required to better understand the impact of lifestyle on the stress and chronic condition trajectory.

Practical implications and future research

Our data indicate that existing health care models need to adapt to the increasing multimorbidity and chronic conditions rates, particularly among the poor. This is especially relevant in LMICs, where all levels of care must be carefully planned in the context of economic restraints. The Innovative Care for Chronic Conditions framework developed by the World Health Organization provides a roadmap to cope with chronic conditions in developing countries but there still is need to fully incorporate multimorbidity and the assessment of perceived stress within primary and mental health care settings (44). First of all, there is a clear need to increase awareness of the importance of considering chronic conditions and perceived stress among primary and mental health care providers in LMICs, and in particular, in socio-economically vulnerable groups (i.e., the poorest). Future research could explore the efficacy and effectiveness of a dual strategy in which both a smaller group of master trainers/supervisors and researchers and a larger group of practitioners (e.g., nurses, occupational therapists) trained in the basics of cognitive behavioral coping strategies and who are supported by regular supervision are involved. This method has been successfully employed for treating depression and psychosis in LMICs in trials (45, 46). Within this stepped-care approach, patients start with self-help. Then, if they do not recover, they progress to working with manualized approaches from a non-specialist worker (e.g., nurses, occupational therapists) who is supervised and are only referred to a specialist (e.g., psychologist, psychiatrist) if there is no improvement as a result of this intervention. However, as stated, careful consideration of which intervention models would be most effective and further research into the therapeutic effectiveness of this stepped-care approach is essential to determine whether there is a need to further develop this therapy for LMICs. Outcomes research including levels of perceived stress but also more distal outcomes such as the risk for chronic conditions and multimorbidity could usefully compare such an approach to more indigenous models of alleviating perceived stress. Longitudinal research is also needed to establish causal associations between common chronic disorders, multimorbidity, perceived stress and poverty; such studies may help identify the specific factors that are associated with the risk of chronic disorders and multimorbidity, and conversely, the factors that help reduce the risk in persons who face severe economic or social adversity. One should note that the

age included in our sample were generally quite young (38.3 years). It is evident that chronic conditions and multimorbidity typically increase with age, also in LMICs (47). Therefore, our finding of a strong relationship between younger adults in LMICs and stress and chronic conditions is concerning. It might by hypothesized that this relationship between stress and chronic conditions becomes stronger with increasing age in LMICs and future research is required to explore this in the context of LMICs.

Strengths and limitations

Strengths of the present study include the use of a very large multi-national data set, focused on LMICs, countries that are under-represented in the existing research literature. The primary limitation is the use of cross-sectional data, which makes it difficult to infer the direction of causality between poverty, heightened perceived stress, higher risk for chronic conditions and multimorbidity. Whereas it is plausible to speculate that the cross-sectional relationships can be best interpreted in the context of poverty being a risk factor for increased perceived stress and consequently chronic disorders and multimorbidity, reverse causality can be a consideration because chronic conditions and multimorbidity are known to produce disability, stress and increased health care costs. In any event, it is more likely that poverty, stress and chronic conditions and multimorbidity interact with one another in setting up, in vulnerable individuals, a vicious cycle. Second, the self-report measure of all chronic conditions and multimorbidity may have led to a bias in the diagnosis of the medical conditions, particularly among older subjects. In addition, whilst we included 11 health conditions (all that were available in the dataset), other health conditions such as stroke and hypertension which are frequently reported in multimorbidity indices (48) may have been present and not identified in the study. Third, it is likely that the sample included in our study suffers from an element of selection bias, in that people with more severe stress, mental or physical health problems may have been less likely to participate in this study. Therefore, our study may actually represent an underestimate of the associations observed. Future research should therefore attempt to include people with more pronounced stress and worse health. Fourth, due to lack of information, we were unable to adjust for factors such as previously experienced trauma which have been associated with both stress sensitivity and chronic conditions (49).

Thus, residual confounding may exist. Fifth, for the purposes of this study, we used an abridged version of the perceived stress scale, which may mean there is some variation in the validity and reliability compared to the original complete scale, and there may also be some psychometric variation across cultures.

In conclusion, our data demonstrate that perceived stress is high among people in LMICs with chronic conditions and multimorbidity. Since perceived stress and chronic conditions are collectively associated with worse outcomes (including increased mortality rates), there is a pressing need to address this issue. Although this may be related to the symptoms of the chronic conditions, the fact that the association was stronger among the poorest points to the possibility that financial factors may also play a role. This may imply that a multidisciplinary approach involving social workers, psychologists, physiotherapists and physicians is needed to decrease stress levels among those with chronic conditions, and this may ultimately lead to better clinical outcomes. Further studies to understand the underlying causes of stress in chronic conditions are warranted.

REFERENCES

1. Fortin M, Stewart M, Poitras ME, et al. A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology. *Ann Fam Med* 2012;10(2):142-151.
2. Uijen AA, van de Lisdonk EH. Multimorbidity in primary care: prevalence and trend over the last 20 years. *Eur J Gen Pract* 2008;14 Suppl 1:28-32.
3. Salisbury C. Multimorbidity: redesigning health care for people who use it. *Lancet* 2012;380(9836):7-9.
4. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012;380(9836):37-43.
5. Lehnert T, Heider D, Leicht H, et al. Review: health care utilization and costs of elderly persons with multiple chronic conditions. *Med Care Res Rev* 2011;68(4):387-420.
6. Fortin M, Lapointe L, Hudon C, et al. Multimorbidity and quality of life in primary care: a systematic review. *Health Qual Life Outcomes* 2004;2:51.
7. Gallo JJ, Hwang S, Joo JH, et al. Multimorbidity, Depression, and Mortality in Primary Care: Randomized Clinical Trial of an Evidence-Based Depression Care Management Program on Mortality Risk. *J Gen Intern Med* 2016;31(4):380-386.
8. Whiteford HA, Degenhardt L, Rehm J, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet* 2013;382(9904):1575-1586.
9. Phillips CA. Perceived stress. In: Gellman MD, Turner JR, eds. *Encyclopedia of Behavioral Medicine*. New York, NY: Springer Science and Business Media; 2013: 1453-1454.
10. Tola HH, Shojaeizadeh D, Garmaroudi G, et al. Psychological distress and its effect on tuberculosis treatment outcomes in Ethiopia. *Glob Health Action* 2015;8:29019.
11. Santiago T, Geenen R, Jacobs JW, et al. Psychological factors associated with response to treatment in rheumatoid arthritis. *Curr Pharm Des* 2015;21(2):257-269.

12. Aikens JE. Prospective associations between emotional distress and poor outcomes in type 2 diabetes. *Diabetes Care* 2012;35(12):2472-2478.

13. Lavoie KL, Bouthillier D, Bacon SL, et al. Psychologic distress and maladaptive coping styles in patients with severe vs moderate asthma. *Chest* 2010;137(6):1324-1331.

14. Russ TC, Stamatakis E, Hamer M, et al. Association between psychological distress and mortality: individual participant pooled analysis of 10 prospective cohort studies. *BMJ* 2012;345:e4933.

15. Prior A, Fenger-Gron M, Larsen KK, et al. The association between perceived stress and mortality among people with multimorbidity: a prospective population-based cohort study. *Am J Epidemiol* [available online ahead of print July 11, 2016]; doi: 10.1093/aje/kwv324.

16. Swartz JA, Jantz I. Association between nonspecific severe psychological distress as an indicator of serious mental illness and increasing levels of medical multimorbidity. *Am J Public Health* 2014;104(12):2350-2358.

17. Murray CJ, Barber RM, Foreman KJ, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition. *Lancet* 2015;386(10009):2145-2191.

18. Leive A, Xu K. Coping with out-of-pocket health payments: empirical evidence from 15 African countries. *Bull World Health Organ* 2008;86(11):849-856.

19. World Health Organization. Health Statistics and Information Systems: WHO World Health Survey. http://www.who.int/healthinfo/survey/en/. Accessed June 15, 2016.

20. Moussavi S, Chatterji S, Verdes E, et al. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet* 2007;370(9590):851-858.

21. Rose GA. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bull World Health Organ* 1962;27:645-658.

22. Freeman EE, Roy-Gagnon MH, Samson E, et al. The global burden of visual difficulty in low, middle, and high income countries. *PloS One* 2013;8(5):e63315.

23. Goldhaber-Fiebert JD, Jeon CY, Cohen T, et al. Diabetes mellitus and tuberculosis in countries with high tuberculosis burdens: individual risks and social determinants. *Int J Epidemiology* 2011;40(2):417-428.

24. Loerbroks A, Herr RM, Subramanian S, et al. The association of asthma and wheezing with major depressive episodes: an analysis of 245 727 women and men from 57 countries. *Int J Epidemiology* 2012;41(5):1436-1444.

25. Cifuentes M, Sembajwe G, Tak S, et al. The association of major depressive episodes with income inequality and the human development index. *Soc Sci Med (1982)* 2008;67(4):529-539.

26. DeVylder JE, Koyanagi A, Unick J, et al. Stress sensitivity and psychotic experiences in 39 low- and middle-income countries. *Schizophr Bull* 2016;42(6):1353-1362.

27. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* 1983;24(4):385-396.

28. Moussavi S, Chatterji S, Verdes E, et al. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *The Lancet* 2007;370(9590):851-858.

29. Nuevo R, Chatterji S, Verdes E, et al. The continuum of psychotic symptoms in the general population: a cross-national study. *Schizophr Bull* 2012;38(3):475-485.

30. Koyanagi A, Stickley A. The Association between Sleep Problems and Psychotic Symptoms in the General Population: A Global Perspective. *Sleep* 2015;38(12):1875-1885.

31. Xu K, Evans DB, Carrin G, et al. Protecting households from catastrophic health spending. *Health Aff (Millwood)* 2007;26(4):972-983.

32. Huffman MD, Rao KD, Pichon-Riviere A, et al. A cross-sectional study of the microeconomic impact of cardiovascular disease hospitalization in four low- and middle-income countries. *PLoS One* 2011;6(6):e20821.

33. Pati S, Agrawal S, Swain S, et al. Non communicable disease multimorbidity and associated health care utilization and expenditures in India: cross-sectional study. *BMC Health Serv Res* 2014;14:451.

34. Makinen M, Waters H, Rauch M, et al. Inequalities in health care use and expenditures: empirical data from eight developing countries and countries in transition. *Bull World Health Organ* 2000;78(1):55-65.

35. Pandey KR, Meltzer DO. Financial Burden and Impoverishment Due to Cardiovascular Medications in Low and Middle Income Countries: An Illustration from India. *PLoS One* 2016;11(5):e0155293.

36. Goldstein DS, McEwen B. Allostasis, homeostats, and the nature of stress. *Stress* 2002;5(1):55-58.

37. McEwen BS. Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. *Eur J Pharmacol* 2008;583(2-3):174-185.

38. McEwen BS. Biomarkers for assessing population and individual health and disease related to stress and adaptation. *Metabolism* 2015;64(3 Suppl 1):S2-S10.

39. Sladek MR, Doane LD, Luecken LJ, et al. Perceived stress, coping, and cortisol reactivity in daily life: A study of adolescents during the first year of college. *Biol Psychol* 2016;117:8-15.

40. Lee E-H. Review of the psychometric evidence of the perceived stress scale. *Asian Nursing Research* 2012;6(4):121-127.

41. Yoon SJ, Kim HJ, Doo M. Association between perceived stress, alcohol consumption levels and obesity in Koreans. *Asia Pac J Clin Nutr* 2016;25(2):316-325.

42. Errisuriz VL, Pasch KE, Perry CL. Perceived stress and dietary choices: The moderating role of stress management. *Eat Behav* 2016;22:211-216.

43. Stults-Kolehmainen MA, Sinha R. The effects of stress on physical activity and exercise. *Sports Med* 2014;44(1):81-121.

44. Oni T, McGrath N, BeLue R, et al. Chronic diseases and multi-morbidity--a conceptual modification to the WHO ICCC model for countries in health transition. *BMC Public Health* 2014;14:575.

45. Naeem F, Sarhandi I, Gul M, et al. A multicentre randomised controlled trial of a carer supervised culturally adapted CBT (CaCBT) based self-help for depression in Pakistan. *J Affect Disord* 2014;156:224-227.

46. Naeem F, Saeed S, Irfan M, et al. Brief culturally adapted CBT for psychosis (CaCBTp): A randomized controlled trial from a low income country. *Schizophr Res* 2015;164(1-3):143-148.

47. Arokiasamy P, Uttamacharya U, Jain K, et al. The impact of multimorbidity on adult physical and mental health in low-and middle-income countries: what does the study on global ageing and adult health (SAGE) reveal? *BMC Med* 2015;13(1):1.

48. Diederichs C, Berger K, Bartels DB. The measurement of multiple chronic diseases—a systematic review on existing multimorbidity indices. *J Gerontol A Biol Sci Med Sci* 2011;66(3):301-311.

49. Tomasdottir MO, Sigurdsson JA, Petursson H, et al. Self reported childhood difficulties, adult multimorbidity and allostatic load. A cross-sectional analysis of the Norwegian HUNT study. *PloS One* 2015;10(6):e0130591.

Table 1 World Health Survey (2002-2004) sample characteristics and mean perceived stress score by each characteristic

Characteristic	Unweighted N	Column %	Mean[a]	95%CI	P-value[b]
Sex					<00001
Male	99,032	49.2	34.7	34.1, 35.2	
Female	121,765	50.8	37.1	36.6, 37.6	
Missing	8,496				
Age (years)					<0.0001
18-29	67,017	37.1	33.1	32.5, 33.7	
30-39	54,332	21.6	35.7	35.1, 36.3	
40-49	40,328	16.9	35.7	35.0, 36.4	
50-59	26,049	11.5	38.3	37.4, 39.2	
60-69	18,248	7.6	40.8	39.7, 41.8	
70-79	10,778	4.2	43.6	42.2, 45.0	
≥80	3,861	1.2	46.7	44.5, 48.9	
Missing	8,680				
Education					<0.0001
No formal	51,193	28.7	44.4	43.7, 45.1	
≤ Primary	71,506	29.6	36.8	36.2, 37.4	
Secondary completed	81,123	32.4	29.1	28.5, 29.6	
Tertiary completed	16,087	9.3	30.4	29.2, 31.7	
Missing	9,384				
Wealth quintile (Individual level)					<0.0001
1 (Poorest)	48,930	20.4	39.2	38.3, 40.0	
2	43,685	20.1	37.7	37.0, 38.4	
3	40,307	19.9	36.1	35.4, 36.9	
4	38,230	19.9	34.5	33.8, 35.3	
5 (Richest)	36,175	19.8	31.8	31.0, 32.6	
Missing	21,966				
Angina					<0.0001
No	187,467	84.9	34.2	33.7, 34.7	
Yes	28,919	15.1	45.4	44.6, 46.1	
Missing	12,907				
Arthritis					<0.0001
No	187,721	86.5	34.5	34.1, 35.0	
Yes	27,284	13.5	44.5	43.7, 45.3	
Missing	14,288				
Asthma					<0.0001
No	205,798	95.7	35.5	35.1, 36.0	
Yes	9,531	4.3	43.4	42.3, 44.6	
Missing	13,964				
Chronic back pain					<0.0001
No	188,731	94.0	35.1	34.6, 35.5	
Yes	10,525	6.0	48.8	47.5, 50.1	
Missing	30,037				
Depression					<0.0001
No	200,977	93.7	34.6	34.1, 35.0	
Yes	12,982	6.3	55.5	54.5, 56.5	
Missing	15,334				
Diabetes					<0.0001
No	193,410	97.3	35.7	35.3, 36.1	
Yes	5,973	2.7	41.8	40.2, 43.5	
Missing	29,910				
Edentulism					<0.0001
No	181,212	95.0	35.7	35.2, 36.1	

Yes	11,917	5.0	39.9	38.7, 41.1	
Missing	36,164				
Hearing problem					<0.0001
No	208,841	96.5	35.5	35.0, 35.9	
Yes	7,084	3.5	47.4	44.9, 49.8	
Missing	13,368				
Schizophrenia					<0.0001
No	211,934	99.0	35.7	35.3, 36.2	
Yes	2,248	1.0	51.3	48.9, 53.6	
Missing	15,111				
Tuberculosis					<0.0001
No	183,938	98.3	35.7	35.3, 36.1	
Yes	3,129	1.7	47.5	45.5, 49.5	
Missing	42,226				
Visual impairment					<0.0001
No	204,300	98.7	35.6	35.2, 36.0	
Yes	2,254	1.3	56.2	53.3, 59.1	
Missing	22,739				
Number of chronic conditions					<0.0001
0	123,935	63.5	31.6	31.1, 32.1	
1	42,978	21.5	39.8	39.1, 40.4	
2	17,298	9.2	45.5	44.7, 46.4	
3	6,777	3.7	50.6	49.0, 52.1	
≥4	3,443	2.1	57.1	55.3, 59.0	
Missing	34,862				

CI=confidence interval. [a]The perceived stress score ranged from 0-100 with higher scores indicating higher levels of perceived stress. [b]The difference in the perceived stress score by sample characteristic was tested by Student's *t*-test and one-way ANOVA for characteristics with two and more than two categories respectively.

Table 2 Interaction Effect of Individual-level Poverty[a] and Chronic Conditions or Number of Chronic Conditions on Perceived Stress[b] (Outcome): Data from the World Health Survey (2002-2004)[c]

	b-coefficient	95%CI	P-value	R^2
Angina				0.19
Main Effect	4.72	3.84, 5.59	<0.0001	
Poverty	2.04	1.11, 2.97	<0.0001	
Interaction	0.80	-0.80, 2.41	0.3263	
Arthritis				0.19
Main Effect	2.99	2.09, 3.89	<0.0001	
Poverty	1.94	1.04, 2.84	<0.0001	
Interaction	1.86	0.23, 3.49	0.0254	
Asthma				0.19
Main Effect	2.73	1.51, 3.94	<0.0001	
Poverty	2.14	1.27, 3.01	<0.0001	
Interaction	2.58	0.31, 4.84	0.0261	
Chronic back pain				0.19
Main Effect	6.82	5.50, 8.15	<0.0001	
Poverty	2.21	1.36, 3.07	<0.0001	
Interaction	0.52	-2.30, 3.34	0.7153	
Diabetes				0.19
Main Effect	2.16	0.45, 3.88	0.0134	
Poverty	2.18	1.32, 3.03	<0.0001	
Interaction	4.20	0.73, 7.66	0.0179	
Depression				0.20
Main Effect	14.60	13.41, 15.79	<0.0001	
Poverty	2.12	1.25, 2.98	<0.0001	
Interaction	0.76	-1.41, 2.93	0.4894	
Edentulism				0.19
Main Effect	-0.17	-1.53, 1.19	0.8065	
Poverty	2.05	1.17, 2.94	<0.0001	
Interaction	3.36	0.78, 5.94	0.0109	
Hearing problem				0.19
Main Effect	5.34	3.45, 7.23	<0.0001	
Poverty	2.11	1.24, 2.98	<0.0001	
Interaction	2.21	-1.39, 5.82	0.2276	
Schizophrenia				0.19
Main Effect	8.86	6.13, 11.59	<0.0001	
Poverty	2.20	1.34, 3.05	<0.0001	
Interaction	4.38	-0.29, 9.05	0.0657	
Tuberculosis				0.19
Main Effect	4.15	1.76, 6.53	0.0007	
Poverty	2.18	1.33, 3.03	<0.0001	
Interaction	2.75	-0.88, 6.38	0.1370	
Visual impairment				0.19
Main Effect	9.35	6.17, 12.53	<0.0001	
Poverty	2.16	1.29, 3.03	<0.0001	
Interaction	4.20	-0.70, 9.10	0.0928	
Number of conditions				
Main effect				0.19
0 Chronic conditions	1.00			
1 Chronic condition	5.38	4.63, 6.12	<0.0001	
2 Chronic conditions	9.39	8.35, 10.44	<0.0001	
3 Chronic conditions	13.46	11.79, 15.13	<0.0001	
≥4 Chronic conditions	19.01	16.67, 21.35	<0.0001	
Poverty	1.45	0.35, 2.56	0.0101	
Interaction				

1 Chronic conditions	1.30	-0.17, 2.78	0.0826
2 Chronic condition	1.15	-0.83, 3.14	0.2552
3 Chronic conditions	2.98	-0.61, 6.57	0.1029
≥4 Chronic conditions	4.45	0.69, 8.21	0.0206

CI=confidence interval. [a]Poverty referred to being in the lowest country-wise individual-level wealth quintile. [b]The perceived stress score ranged from 0-100 with higher scores indicating higher levels of perceived stress. [c]All estimates are adjusted for sex, age, education, other illnesses, and country.

Figure legends

Figure 1. Perceived Stress Score by the Number of Chronic Conditions and Individual-level Wealth Quintiles

Estimates are based on weighted sample. The perceived stress score ranged from 0 to 100 with higher scores indicating higher levels of perceived stress.

Figure 2. Association Between Chronic Conditions and Perceived Stress (Outcome) Estimated by Multivariable Linear Regression

Abbreviation: CI confidence interval. All estimates are adjusted for sex, age, education, individual-level wealth, other illnesses, and country. Each chronic condition was assessed individually in separate models. The perceived stress score ranged from 0 to 100 with higher scores indicating higher levels of perceived stress. $P<0.001$ for all associations with the exception of edentulism ($P=0.2846$).

APPENDIX.
Countries Included in the Analysis and Their Sample Size

Country	Unweighted N
Bangladesh	5,942
Bosnia Herzegovina	1,031
Burkina Faso	4,948
Chad	4,870
China	3,994
Comoros	1,836
Croatia	993
Czech Republic	949
Dominican Republic	5,027
Ecuador	5,675
Estonia	1,020
Ethiopia	5,089
Ghana	4,165
India	10,687
Ivory Coast	3,251
Kazakhstan	4,499
Kenya	4,640
Laos	4,988
Latvia	929
Malawi	5,551
Malaysia	6,145
Mali	4,886
Mauritania	3,902
Mauritius	3,968
Mexico	38,746
Morocco	5,000
Myanmar	6,045
Namibia	4,379
Nepal	8,820
Pakistan	6,501
Paraguay	5,288
Philippines	10,083
Republic of Congo	3,075
Russia	4,427
Senegal	3,461
Slovakia	2,535
South Africa	2,629
Sri Lanka	6,805
Swaziland	3,117
Tunisia	5,202
Ukraine	2,860
Uruguay	2,996
Vietnam	4,174
Zambia	4,165